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Emerging pharmacotherapy for COVID-19

Brian Lipworth¹, Chris RuiWen Kuo², Rory Chan³

Abstract

Broadly speaking, pharmacological treatments for COVID-19 can be divided into those acting on upstream pathways early on in the disease process via suppression of viral replication or by inhibiting cell entry, and those acting on downstream pathways later on via selective attenuation of the adaptive immune cytokine-mediated inflammatory response. The antiviral drug remdesivir has been shown to shorten duration of disease while interferon

beta-1b may speed up viral clearance. The results with hydroxychloroquine have thus far been rather disappointing. Trials with selective cytokine blockers including anti-interleukin-1 (anti-IL-1) and anti-interleukin-6 (anti-IL-6), have shown some promise in more severe cases, with further confirmation being required from large-scale phase-3 randomised controlled trials. The likelihood is that combination therapy addressing both upstream and downstream pathways may be required to prevent progression of severe COVID-19 infection in susceptible older patients with comorbidities and we believe further studies are now warranted to specifically target such at-risk groups who are more prone to worse outcomes.

Keywords: COVID-19, SARS-CoV-2, pneumonia, cytokine, hyperinflammation, antivirals, ACE2, TMPRSS2, ARDS, corticosteroid, comorbidity

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Introduction

The landscape of COVID-19 and related therapies is a fast changing area of research. It now seems timely to synthesise some emerging trends and speculate about key future directions in COVID-19 pharmacotherapy given that we are unlikely to have an effective vaccine in the near future.

After initial infection via the nose with SARS-CoV-2 the virus rapidly spreads to the lungs to cause severe hypoxic pneumonia. In some susceptible individuals this may be accompanied by an exaggerated adaptive immune response involving a cytokine cascade and associated hyperinflammatory syndrome,¹ followed by the development of acute respiratory distress syndrome (ARDS), assisted ventilation and ultimately death. In many respects, the later stages of severe COVID-19 infection manifests as a multi-organ viral-induced type of autoimmune disease (Figure 1). This inflammatory process may be accompanied by a pronounced intravascular coagulopathy with elevated D-dimers, which may further aggravate ventilation-perfusion mismatch and

worsening hypoxaemia.² Hence low molecular weight heparin has been proposed to prevent thromboembolism.

In the earlier stages of COVID-19 infection one might expect antiviral strategies to be more effective on the upstream disease pathway. In the later stages, once cytokine-related hyperinflammation sets in, strategies to selectively suppress the immune response on the downstream pathway are more cogent (Figure 2).¹ Patients who fare worst tend to be elderly, males, Black or Asian, smokers, obese, those with comorbidities such as chronic lung disease, diabetes, chronic heart disease, hypertension, dementia, chronic kidney disease, as well as those with neoplasia and immunosuppression.³

Upstream strategies

Initial interest inevitably focussed on antiviral therapies to arrest replication of SARS-CoV-2 with the aim of lessening the burden of viral load. In a randomised controlled trial (RCT) of

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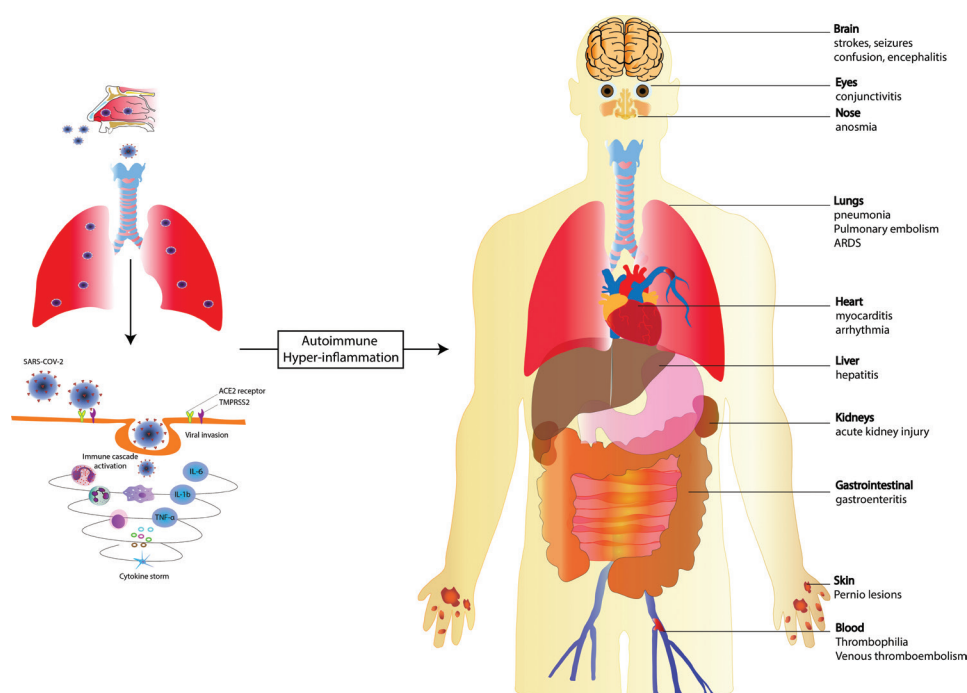


Figure 1 Depicts the concept of multi-organ viral-induced autoimmune disease with severe COVID-19 associated cytokine-mediated hyperinflammation. ACE2: angiotensin converting enzyme-2, TMPRSS2: transmembrane protease serine 2 enzyme, NSP15: nonstructural protein 15, SARS-CoV-2: severe acute respiratory syndrome coronavirus-2

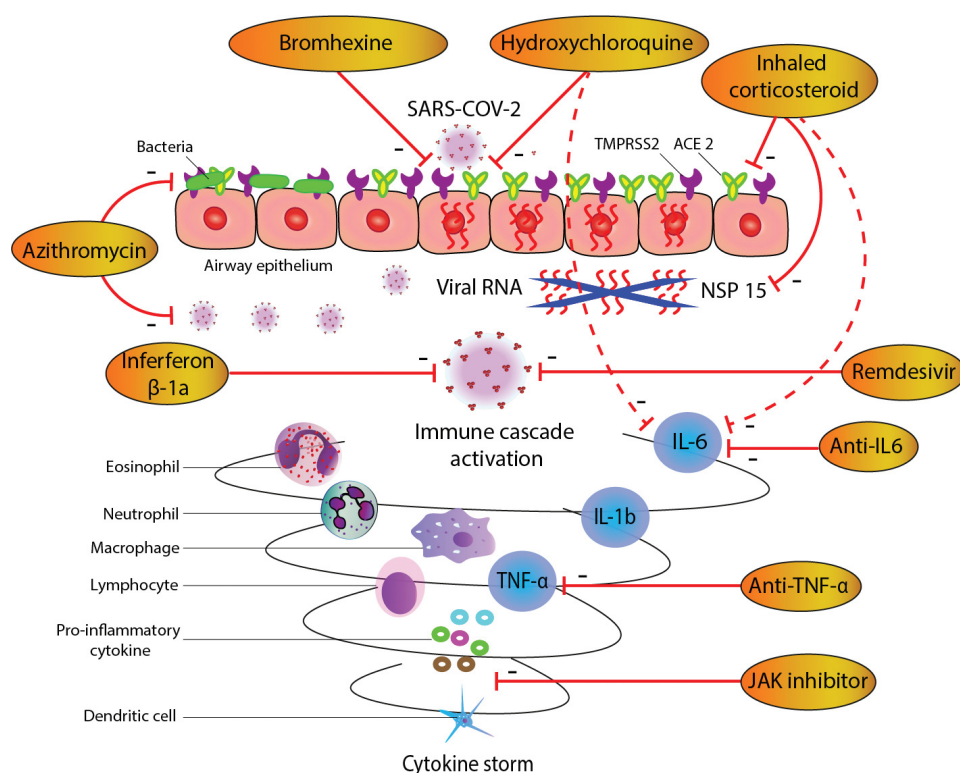


Figure 2 Depicts the potential upstream (suppression of viral replication and inhibition of cell entry) and downstream (selective anti-cytokine) pharmacological targets for COVID-19. IL: interleukin, TNF: tumour necrosis factor, JAK: Janus kinase, ACE2: angiotensin converting enzyme 2, TMPRSS2: transmembrane protease serine 2 enzyme, NSP15: nonstructural protein 15, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

199 patients with severe COVID-19, the combination of oral lopinavir/ritonavir was no more effective than standard of care (SOC) for the primary endpoint (PEP) of time to clinical improvement.⁴ In mild to moderate COVID-19 triple antiviral therapy comprising interferon beta-1b, ribavirin with lopinavir/ritonavir, but not dual therapy without interferon beta-1b, significantly shortened the duration of nasopharyngeal viral shedding by five days and alleviated symptoms compared to lopinavir/ritonavir alone.⁵

A RCT comparing intravenous (IV) remdesivir with placebo in 237 severe COVID-19 patients found no significant difference in the PEP of time to clinical improvement or in mortality, although the trial had only 58% power due to premature termination.⁶ Preliminary data from 397 patients with severe COVID-19 found that 5 or 10 days of treatment with IV remdesivir were equally effective, although no control group was included.⁷ Interim analysis of data from the National Institute of Allergy and Infectious Diseases in the USA comparing IV remdesivir to placebo in 1063 patients with severe COVID-19 revealed a significantly shorter median

recovery time amounting to four days but no significant difference in deaths at 14 days (7.1% vs 11.9%).⁸ On the basis of this result, the USA Food and Drug Administration granted authorisation for emergency use of remdesivir for severe COVID-19, and by the European Medicines Agency for compassionate use in patients not on mechanical ventilation. Azithromycin (AZI) also has putative antiviral activity, as well as downstream immune-modulating effects on cytokines and has been included in the UK National Institute of Health Research (NIHR) primary and secondary care trials.

Much publicity has surrounded the potential use of hydroxychloroquine (HCQ). It acts upstream by arresting endocytic host-cell entry of SARS-CoV-2 into type 2 pneumocytes, attaching via angiotensin-converting enzyme 2 (ACE2). In addition, HCQ also has a downstream effect by inhibiting release of the proinflammatory cytokines including interleukin-6 (IL-6). One RCT in 36 hospitalised patients treated with HCQ reported a significant reduction in viral load compared to controls.⁹ In an open label randomised trial of 150 mild to moderate COVID-19, use of HCQ led to a similar probability for the PEP of virus elimination compared to SOC.¹⁰ A comparative observational trial of HCQ in 181 hypoxic severe COVID-19 patients showed no significant impact compared to SOC on the PEP of survival without transfer to intensive care on day 21, while 10 % of patients had HCQ stopped due to prolongation of the QTc interval.¹¹ A pragmatic observational study of 1376 patients from New York City showed no significant difference in the PEP of death or intubation after propensity score weighting, amounting to a 4% difference comparing patients who were taking to those not taking HCQ, although patients taking HCQ had worse oxygenation and higher CRP levels at baseline.¹² Furthermore, there was no significant association with concomitant use of AZI and the PEP. It should be appreciated that QTc prolongation with HCQ may be aggravated by co-administration with AZI and therefore electrocardiogram monitoring should be performed when both drugs are given concomitantly.¹³ As it stands, the present evidence does not support use of HCQ in either early or late stage COVID-19.

Cell uptake of zinc may be augmented by combining with an ionophore such as HCQ. In 933 hospitalised patients the addition of zinc to HCQ/AZI resulted in significantly improved outcomes as a 33% increased likelihood of patients being discharged from hospital and a 45% lower likelihood of need for intensive care or intubation.¹⁴

Much larger pragmatic RCTs have embraced HCQ including NIHR trials in primary care as monotherapy (PRINCIPLE) and in secondary care as either monotherapy or in combination with the anti-IL-6 agent tocilizumab (RECOVERY) or with antivirals (REMAP-CAP).

Blocking viral cell entry via transmembrane protease, serine 2 enzyme (TMPRSS2)¹⁵ is another possibility, using the cough remedy bromhexine given alone or in combination with HCQ (NCT04340349, NCT04355026, NCT04273763). Notably, inhaled corticosteroids (ICS) have also been found to reduce

gene expression of ACE2 and TMPRSS2 receptors in sputum cells of asthma patients, which might confer protection against progression of COVID-19 infection.¹⁶

Downstream strategies

Circulating maximal levels of IL-6 above 80 pg/ml are associated with a 22-fold increased risk of impending respiratory failure in severe COVID-19 patients, being indicative of hyperinflammatory syndrome.¹⁷ Another cohort reported that IL-6 above 32 pg/ml and CRP above 42 mg/l at initial presentation were indicative of worse clinical outcomes.¹⁸

Early attention has focussed on repurposing anti-IL-6 agents, namely tocilizumab and sarilumab which are indicated for rheumatoid disease. Uncontrolled data from compassionate use of tocilizumab as a single subcutaneous 400mg dose in 21 patients with severe COVID-19 showed improvements within five days in fever, CRP, lymphocyte counts, imaging infiltrates and oxygenation, with 90% of cases being discharged within a mean period of 13.5 days after administration.¹⁹ An early analysis of preliminary phase-2 RCT data in 457 hospitalised COVID-19 patients showed that IV sarilumab 200mg or 400mg compared to placebo significantly lowered the PEP of CRP levels but had no overall clinical benefit in combined severe or critical patient groups.²⁰ Post hoc exploratory analysis of the 400mg dose in critical patients showed a 23% absolute difference in patients who either died or were being ventilated, 18% difference for those who showed clinical improvement, 12% difference in patients able to wean off oxygen, and 29% difference in those who were discharged from hospital. Other placebo RCTs are evaluating tocilizumab alone or in combination with antivirals: RECOVERY, COVACTA (NCT04320615) and TOCOVID (NCT04322773 and NCT04310228).


Systemic corticosteroids exhibit non-selective immunosuppressive effects and thus far have shown no improvement in severe COVID-19 outcomes, perhaps in part due to the possibility of inducing secondary bacterial and fungal infections.²¹ However, recent interest has centered on using ICS as a potential strategy for earlier intervention. ICS exhibit protective class effects by attenuating viral cell-entry as well as inhibiting downstream IL-6.^{16,22} In addition, there is a specific ICS effect conferred by ciclesonide and mometasone, but not budesonide, beclomethasone or fluticasone, via nonstructural protein 15 which results in attenuated replication of SARS-CoV-2 in vitro.²³ In South Korea, a study using ciclesonide will evaluate SARS-CoV-2 eradication in patients with mild COVID-19 infection (NCT04330586).

Other downstream selective immune modifiers which are being investigated include anti-IL-1, anti-tumour necrosis factor and selective Janus kinase (JAK) inhibitors. An uncontrolled trial in 45 hospitalised COVID-19 patients with the anti-IL-1 agent IV anakinra at high dose showed a significant 34% difference in survival after 21 days when compared to a retrospective standard of care group, but no difference in mechanical ventilation-free survival.²⁴

Next Steps

It remains to be seen if either antivirals or blockers of viral cell entry can be used for effective secondary prevention in early-stage infection to modify the severity of COVID-19. It is very unlikely that a single agent will prove to be the 'magic bullet' in later stage severe COVID-19. Hence combinations of upstream and downstream disease modulators may be required as either dual or triple therapy.¹ Using biomarkers such as IL-6 or CRP should help to identify hospitalised patients with hyperinflammatory syndrome at greater risk of respiratory failure who may need escalation of treatment. Future clinical trials should be focussed on preventing susceptible older patients with comorbidities from developing severe outcomes.

Key Messages

- Severe COVID-19 manifests as a viral-induced multisystem autoimmune disease characterised by an adaptive cytokine-mediated immune response with associated hyperinflammation and coagulopathy
- Elevated biomarkers such as IL-6 and CRP indicate worsening hyperinflammation and impending respiratory failure with a commensurate need to escalate therapy
- Combination therapy addressing upstream and downstream pathways, for example using antivirals with selective cytokine inhibitors, may be required to prevent progression of severe COVID-19 infection
- Randomised controlled trials need to be targeted at susceptible older individuals with comorbidities who tend to have worse outcomes associated with COVID-19 

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